



Continuing Medical Education

Glucocorticoids in Rheumatoid Arthritis: Almost Always or Hardly Ever? ☆☆☆

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ABSTRACT

The use of glucocorticoids in rheumatoid arthritis has been the source of frequent debate in the last few decades. There is evidence on its anti-inflammatory capacity and its power to decrease radiologic progression, particularly if used in recent onset rheumatoid arthritis. However, there are still some voices questioning its use. Their arguments are its potential side-effects, especially when the glucocorticoids are used in high doses and/or for extended periods of time.

In this review, we will try to summarize the evidence regarding this issue, from the beginning of the discussion in the fifties to the last releases.

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Glucocorticoides en artritis reumatoide: ¿casi siempre o casi nunca?

RESUMEN

El uso de los glucocorticoides en la artritis reumatoide ha sido objeto de debate en las últimas décadas. Parece existir evidencia probada, en cuanto a su capacidad antiinflamatoria y su poder de disminuir la progresión radiológica, principalmente si se utiliza en artritis reumatoide de inicio reciente. Sin embargo, sigue cuestionándose su uso debido a sus potenciales efectos secundarios, sobre todo cuando se utilizan en altas dosis y/o durante periodos prolongados.

En esta revisión, intentaremos resumir la evidencia existente sobre este aspecto desde los inicios, allá por los años 50, hasta las últimas publicaciones.

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Introduction

Since the use of cortisone (or substance E) by Hench in 1949 on a 29-year-old established rheumatoid arthritis patient (with immediate symptomatic improvement on the one hand, but important side effects on the other), a great variety of articles have been published regarding this question.

During the past few years there is a widely extended tendency to consider some glucocorticoids as disease-modifying drugs, something that we will also attempt to analyze here.

Almost Always...

Among the benefits derived from the use of steroids in rheumatoid arthritis we find clinical improvement, delay in radiographic progression and a better quality of life. We will distinguish between two different scenarios: early rheumatoid arthritis and established rheumatoid arthritis.

Early Rheumatoid Arthritis

In 1959¹ the first article suggesting a disease-modifying role of steroids on rheumatoid arthritis was published. It was a randomized clinical trial comparing patients with disease for less than 2 years and compared the use of prednisone vs aspirin/phenylbutazone. After two years of follow-up, patients receiving steroids had earlier clinical improvement and functional improvement and, at the same time, less radiologic progression.

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Kirwan,² in 1995, in a multicentric, controlled, randomized, double blind trial concluded that early and active rheumatoid arthritis benefited from the administration of low dose prednisone along with other disease-modifying drugs by reducing radiologic progression, when compared to placebo. However, another two randomized and controlled trials published the same year did not find any statistically significant superiority in patients receiving steroids. Van Schaardenburg et al.,³ studied a population of patients over 60 with rheumatoid arthritis with a mean time since onset of 11 months and compared the use of prednisone (15 mg) vs cloroquine; Van Gestel et al.,⁴ studied rheumatoid arthritis with less than 30 weeks since onset of disease and compared prednisone (10 mg) vs placebo/gold salts. One must consider that the study by Kirwan et al., by comparing initial demographic characteristics in both treatment groups, showed a significantly higher degree of baseline radiologic damage in the placebo group, with a Larsen score of 6.23 vs 2.65 in the group treated with prednisone. Hickling et al.,⁵ a year after that, proved the persistence in the reduction of radiological damage in the group initially treated with prednisone.

Another study supporting the capacity of steroids as inhibitors of radiological damage is the COBRA⁶ trial, a multicentric, randomized, double blind study comparing, in patients with rheumatoid arthritis and a mean time since onset of 4 months and an 80-week intervention, a triple therapy composed by prednisolone, sulphasalazine, and methotrexate vs sulphasalazine monotherapy. At week 28, ACR20 (72% triple therapy; 49% monotherapy) and ACR 50 (49% triple therapy; 27% monotherapy) were measured. In regard to joint destruction, results in both groups as measured by the modified Sharp score were higher in the combined therapy group at weeks 28, 56, and 80. The study concluded that triple therapy allows for a better control of disease and this improvement persists for one year after suspension of prednisone. After follow-up, at 4⁷ and 11⁸ years after its completion, there is evidence which supports a continuing reduction in radiographic progression in the triple therapy group compared to the monotherapy group, independently of treatment received afterward. Taking into account that no differences have been seen in studies comparing combined methotrexate and sulphasalazine therapy vs sulphasalazine monotherapy, we may conclude that the addition of steroids is responsible for the reduction in radiological damage seen in the triple therapy group.

The study by Van Everdingen et al.⁹ in 2002, a multicentric, randomized, double blind clinical trial is considered as high in quality. In it, prednisone (10 mg) is compared to placebo, allowing the use of sulphasalazine as a rescue drug after the first 6 months in patients who had previously not used a DMARD, with rheumatoid arthritis of less than one year since onset. Patients in the prednisone group showed clinical benefit in the first 6 months, after which there was only statistical superiority in the tender joint count and the grip strength. Benefit regarding structural damage persisted even after 2 years after the end of the study.¹⁰

In 2005 saw the publication of two clinical trials, both multicentric, randomized, double blind, which support both clinical and radiographic benefits of steroids in early rheumatoid arthritis. Wassenberg et al.¹¹ compared prednisone (5 mg) vs placebo in patients with rheumatoid arthritis of less than 2 years since onset, starting treatment with methotrexate/gold salts. Svensson et al.¹² compared the addition of DMARD to prednisone (7.5 mg) vs placebo in patients with rheumatoid arthritis of less than one year since onset, with no previous DMARD use. Both studies show a reduction of radiographic progression in the intervention group. In addition, the BARFOT trial showed a greater percentage of remission after 2 years in the prednisone group (55% vs 32.7%). In 2008, Hafström et al.,¹³ in an open study, proved that patients in the

prednisone group had less radiographic progression when compared to patients with remission vs patients with active disease.

The BEST¹⁴ study was designed to evaluate the optimal treatment strategy to prevent radiological damage and lead to a better functional status in early rheumatoid arthritis. This is a randomized multicenter study, which compared four treatment strategies: group 1 (sequential monotherapy DMARD), group 2 (step-up therapy), group 3 (similar to the COBRA study triple therapy: prednisone, methotrexate and sulfasalazine), and group 4 (infliximab and methotrexate). The patient follow-up was one year, and during the follow-up reviews, treatments were modified according to a pre-established pattern for each group. With regard to functional status, groups 3 and 4 (initial combination therapy) showed a more rapid improvement as measured by the Health Assessment Questionnaire (HAQ). The maintenance of the Disease Activity Score (DAS) 44 less than or equal to 2.4, which defines low disease activity was as follows: 53%, 64%, 71%, and 74% for groups 1, 2, 3, and 4, respectively. The study concludes that initial combination therapy provides an early functional improvement with a reduction of radiological progression.

The TICORA¹⁵ study was a single-blind, randomized, controlled trial designed to evaluate an intensive therapeutic strategy against a routine one in rheumatoid arthritis with an average duration of 19 months. In the intensive group a monthly visit was carried out which measured disease activity, and intra-articular corticosteroids were administered in all inflamed joints that had not been infiltrated in the past 3 months. It allowed a maximum of three local infiltrations (corresponding to 120 mg of triamcinolone) for each visit. If during the first 3 months of starting a new DMARD, patients had not received the 120 mg intraarticular triamcinolone, they were administered an intramuscular equivalent dose if the DAS was greater than 2.4. This study found that intensive management provides better results in terms of disease activity, quality of life and radiographic progression, with no additional costs. In 2007,¹⁶ a systematic review was published that was aimed to assess the effectiveness of glucocorticoids in inhibit radiographic progression in rheumatoid arthritis. To this end, randomized controlled or crossover trials that compared corticosteroids vs placebo or active controls and where outcomes obtained radiographs of hands, feet or hands, feet by any standard technique were analyzed. At least one arm had to be with glucocorticoids and one without. Most of the studies included (15 studies, 1414 patients) had patients with rheumatoid arthritis of less than 2 years. In all cases, glucocorticoids are mostly added to other disease-modifying drugs. The results of the meta-analysis were as follows. In terms of erosion, all studies except one¹⁵ revealed a numerical effect in favor of glucocorticoids. The standardized mean difference (SMD) in the progression was 0.39 in favor of glucocorticoids (95%CI 0.27–0.54). As for the reduction of joint space, only seven studies included it and it was also statistically significant in favor of the use of glucocorticoids with a SMD for change at one year of 0.36 (95%CI 0.18–0.53). There was a significant decrease in the progression of erosions at 1 and 2 years in all subgroups analysis. The authors concluded “by the most conservative estimate, there is evidence that glucocorticoids given in addition to standard therapy can significantly reduce radiographic progression in rheumatoid arthritis.”

Established Rheumatoid Arthritis

Two well-known meta-analysis conducted in established rheumatoid arthritis compared the use of glucocorticoids with placebo or NSAIDs. Gøtzsche and Johansen,¹⁷ published in 1998 a systematic review whose objective was to determine whether low

doses of oral corticosteroids (maximum 15 mg of prednisolone or equivalent per day) in the short term (a month) are superior to placebo and NSAIDs. To do this, 10 trials were included with a total of 320 patients, using SMD as outcome measures. The results showed statistically significant superiority of glucocorticoids in terms of joint tenderness and pain, versus placebo and NSAIDs, as well as grip strength compared to placebo. The authors conclude that “while prednisolone is highly effective, no placebo-controlled trials to analyze short-term clinical effect of low doses of oral prednisolone or other glucocorticoids were found.” In 1996, Criswell et al.¹⁸ sought to determine the effectiveness in the medium term (at least 3 months) of low-dose oral corticosteroids (mean dose below 15 mg per day prednisolone or equivalent) for the treatment of rheumatoid arthritis. To do this they conducted a systematic review that included randomized or crossover studies with at least one quantitative measure of pain, swelling, grip strength or ESR; the control group could be placebo or active drug and SMD was used as outcome measures. Seven studies were included, where 253 patients received glucocorticoids, 177 placebo, 50 aspirin, and 28 chloroquine. Glucocorticoids were statistically significantly higher over placebo in tender and swollen joints counts, pain and functional capacity. They found no such differences regarding aspirin or chloroquine.

New Evidence

The use of glucocorticoids in rheumatoid arthritis is currently still under investigation. We highlight some articles that refer to this issue. Todoerti et al.¹⁹ have been trying to determine the rate and duration of remission by adding low doses of steroids to a therapeutic step-up DMARD versus placebo in rheumatoid arthritis patients under 1 year. They have concluded that the use of corticosteroid therapy in rheumatoid arthritis is associated with higher remission rates and longer clinical remission, as well as an early control of the activity. Two other studies published this year in early inflammatory polyarthritis report very different conclusions. In the SAVE²⁰ study, it has been found that an intramuscular dose of glucocorticoids in early arthritis (<16 weeks) does not induce remission, and postpones the development of rheumatoid arthritis or the beginning of DMARD. However, the STIVEA²¹ study argues that the treatment of patients with early inflammatory polyarthritis (4–10 weeks) with three weekly doses of intramuscular steroids seems to postpone the start of DMARD and prevents progression to rheumatoid arthritis in 1 of every 10 patients. Graudal and Jürgens²² in their meta-analysis set out to determine the differences in the effect on joint destruction in rheumatoid arthritis patients of DMARD monotherapy and combination therapy, glucocorticoids and biological treatment, measuring the annual radiographic progression rate. They conclude that DMARD, glucocorticoids, biologics, and combinations between them decrease radiological progression per year. It is also remarkable that a direct comparison between treatments (biological+DMARD and two DMARD+glucocorticoids) showed no difference.

Recommendations

Given the central role of steroids in the treatment of rheumatoid arthritis there are a number of recommendations created by interdisciplinary groups based more or less on consensus, which we can use to guide us in our clinical practice. Thus we have the latest EULAR²³ recommendations, published this year, on the use of glucocorticoids in rheumatoid arthritis. A systematic review aimed to answer five questions on this issue, was conducted and which we summarize here. With grade IB evidence, it claims that

direct and indirect data provide evidence that glucocorticoids can be used effectively as bridge therapy. In addition, there are benefits in adding steroids to DMARD monotherapy (IB evidence) or combined DMARD (IIB evidence). The addition of corticosteroid therapy (<7.5 mg per day of prednisone or equivalent) to standard therapy with DMARDs in rheumatoid arthritis reduces radiographic progression onset, while in established rheumatoid arthritis, the addition of glucocorticoids (<15 mg per day) leads to an improvement in disease activity (evidence IA). Another issue being studied in recent years is timing. It seems that the use of modified preparations and the night administration of glucocorticoids improve morning stiffness (evidence IB). To have the best strategy for decreasing doses of glucocorticoids, there is only indirect information that suggests that it should be done slowly to avoid relapse (evidence IV). Other recommendations on the use of glucocorticoids in clinical practice recently published are those of Mouterde et al.²⁴ (which include the various forms of oral steroids given according in different stages of rheumatoid arthritis) and those of Dernis et al.²⁵ (which includes the recommendations for the use of bolus of glucocorticoids and intra-articular injections).

Disease-Modifying Drugs

To be defined as disease-modifying drug, the following characteristics must be present: ability to control the disease, reduce joint damage and improve long-term results. Due to all of this, and taking into account of revised data it is not far fetched to consider glucocorticoids as disease-modifying drugs. In fact, there is a tendency in the last decade to have this question settled, and authors like Buttgerit²⁷ and Bijlsma et al.²⁶ point their article in this direction. The 2008 recommendations of the ACR²⁸ on the use of synthetic disease-modifying/biological drugs in rheumatoid arthritis included glucocorticoids in the category of ‘anti-inflammatory drug interventions’. This led to an editorial by Van Tuyl et al.,²⁹ arguing that, for a guide for rheumatoid arthritis therapy to be complete, it should include steroids and disease-modifying drugs. Saag et al. responded acknowledging that this issue was one of the limitations of their study and confirmed that future updates would be a topic for discussion. The EULAR³⁰ recommendations published this year on DMARDs and biological management in rheumatoid arthritis does include glucocorticoids in the sixth recommendation, where we can read, “glucocorticoids have anti-inflammatory and disease-modifying action.”

Hardly Ever . . .

Side Effects

Many of the side effects are attributed to the use of glucocorticoids, and this is the main limitation for using them in rheumatoid arthritis. However, apart from weight gain and cutaneous effects, such as skin atrophy and alopecia, there is not much difference compared to placebo. As for one of the most controversial issues, osteoporosis, studies provide very different results, but fortunately we can use different protocols for its prevention and treatment. With regard to cardiovascular side effects, currently a hot topic, there is no evidence that low doses of corticosteroids, unlike high doses, increase the incidence of cardiovascular disease. In this case it is also important to monitor the effect of glucocorticoids on CRP and research their role in heart disease. Here we refer to three meta-analyses. The study of Da Silva et al.,³¹ published in 2006 is based on four randomized, controlled clinical trials conducted in patients with rheumatoid arthritis and with low doses of oral

glucocorticoids, with the following conclusion: “Registered safety data suggest that associated adverse effects are modest and very often not statistically significant compared to placebo. The meta-analysis by Hoes et al.³² studied the adverse effects associated with oral corticosteroids at doses below 30 mg of prednisone or equivalent per day, for at least 1 month in three types of inflammatory diseases: rheumatoid arthritis, polymyalgia rheumatica, and inflammatory bowel disease. In the group of patients with rheumatoid arthritis, follow-up was longer and was associated with lower rates of adverse effects. It concluded that “adverse effects depend on the design of the study and the underlying disease.” The aim of the meta-analysis of Ravindran et al.³³ was to measure the toxicity associated with the use of low doses of glucocorticoids in rheumatoid arthritis on the medium to long term (over 1 year) and was based on 6 randomized, controlled, double-blind, placebo-controlled studies. Using the odds ratio (OR) as an outcome, it yielded the following results: number of losses due to adverse effects (OR: 1.09 with 95%CI 0.52–2.25), number of effects adverse patient per year (OR: 1.19 with 95%CI 0.91–1.57), serious adverse events (OR: 1.06 with 95%CI 0.67–1.67). The study concluded “treatment with glucocorticoids in the medium to long term is associated with limited toxicity compared to placebo.”

Conclusions

As to the question “Glucocorticoids in rheumatoid arthritis: almost always or hardly ever?” it seems reasonable to opt for the former. There is sufficient scientific evidence on the benefits of glucocorticoids in rheumatoid arthritis based on clinical, functional and structural grounds. For this reason, their integration as disease-modifying drugs should be reconsidered. On the other hand, more studies on the adverse effects attributed to glucocorticoids are required, since the majority of existing ones are observational and short-term. Fortunately, to ensure safety in their use, we have recommendations that support clinical practice.

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